* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = NR8COR9, NR8CO2R9, NR8CON(R9)2, COR9, CO2R9, CON(R9)2; R2 = OR9, N(R9)2; R3 = H, halo, OH, protected-OH, NH2, protected-NH2, alkyl, haloalkyl; R4-5 = R9, OR9, N(R9)2, N=NR9, R4, R5 may together form =O, =C(R8)2, NR10 or R4-5 together with the carbon to which they are both attached form spiro carbocyclic or heterocyclic ring; R6 = H, inorg. groups having 1-8 atoms selected from boron, sulfur, phosphorous, silicon, hydrogen, and org. groups having 1-20 carbons, optionally contg. 1-4 heteroatoms selected from nitrogen, oxygen and silicon; R7 = halo, OH, protected-OH, NH2, protected-NH2, alkyl, haloalkyl; R8 = H, alkyl, aryl, heteroalkyl; R9 = H, org. groups having 1-30 carbons with the provision that two R9 groups both joined to common atom may be joined together so as to form ring with the common atom; R10 = R9, OR9, N(R9)2, NHCOR9; NHCOOR9, NHCSNHR9; n is 0-2; with the proviso that when R6 = H, R4-5 together form =O and R1 = CO2R2, then R2 is not OCH3] were prepd. For instance, 2,7-dihydroxynaphthalene was reacted with maleic anhydride (1,2-dichlorobenzene/PhMe, 110.degree.C, 3 days) to afford the bicyclobenzocyclobutane adduct (16% yield). This anhydride was reacted with 2-(trimethylsilyl)ethanol affording a 1:1 mixt. of regio isomers which was isolated as the dicyclohexylamine (DCA) salt (93% yield). The DCA salt was treated with 2M HCl permitting the isolation of the free regioisomers which were then converted to the isopropylamine salts and crystd. affording the desired regioisomer as a 87/16 mixt. Further crystn. and liberation of the acid ester afforded II as a white solid in 30% overall yield with 98.2% purity by HPLC. Also described is a process of prepg. a combinatorial library of I from III [linker = e.g., O-CH2-C6H5-O-CH2CONH; SS = solid support; PG1 = protecting group, e.g., O-allyl; PG2 = protecting group, e.g., OCH2CH2TMS]. The method involves removal of PG1 (PG1 = O-allyl, (Ph3)4Pd/N-methylaniline) in the presence of PG2 (PG2 = OCH2CH2TMS, TBAF) and subsequent amidation with a plurality of amines; removal of PG2 and amidation with a plurality of amines and removal of the linker (TFAaq) to liberate the corresponding bis(amides). A library of 1152 bis(amides) were prepd. in this manner. Compds. of the invention were evaluated for inhibition of apoptosis and NF.kappa.B. I are useful for inhibiting cellular events involving TNF-.alpha. and IL-8, and in the treatment of inflammation events in general.

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ACCESSION NUMBER: 2002:504796 CAPLUS
DOCUMENT NUMBER: 137:78768
TITLE: Preparation and use of benzobicyclobutanes as inhibitors of TNF-.alpha., IL-8 and for treating inflammation
INVENTOR(S): Jackson, Randy W.; Darwish, Ihab; Baughman, Ted A.; Howbert, J. Jeffry
PATENT ASSIGNEE(S): Celltech R & D, Inc., USA
SOURCE: PCT Int. Appl., 200 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
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WO 2002051851	A3	20030123		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,

CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003069305 A1 20030410 US 2001-15828 20011211

PRIORITY APPLN. INFO.: US 2000-257532P P 20001222

OTHER SOURCE(S): MARPAT 137:78768

IT **439798-63-7P 439798-84-2P**

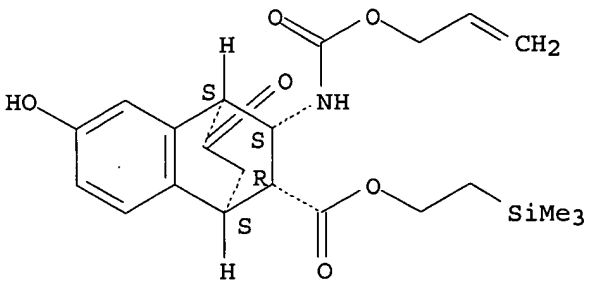
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(drug; prepn. of benzobicyclobutanes derived from Diels-Alder adduct of 2,7-dihydroxynaphthalene and maleic anhydride as inhibitors of TNF-.alpha., IL-8)

RN 439798-63-7 CAPLUS

CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6-hydroxy-9-oxo-3-[[(2-propenyloxy)carbonyl]amino]-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3R,4R)-rel- (9CI) (CA INDEX NAME)

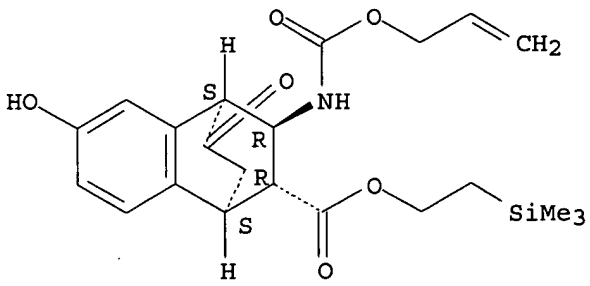
Relative stereochemistry.



RN 439798-84-2 CAPLUS

CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6-hydroxy-9-oxo-3-[[(2-propenyloxy)carbonyl]amino]-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **439798-80-8P 439798-81-9P 439798-82-0P**
439798-83-1P 439798-85-3P 439798-86-4P
439798-87-5P 439798-88-6P 439798-89-7P
439798-90-0P 439798-91-1P 439799-36-7P
439799-37-8P 439799-80-1P 439800-25-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

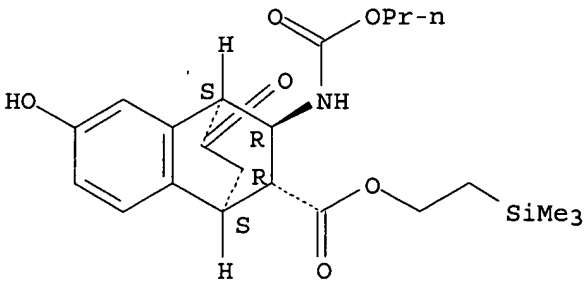
(drug; prepn. of benzobicyclobutanes derived from Diels-Alder adduct of 2,7-dihydroxynaphthalene and maleic anhydride as inhibitors of TNF-.alpha., IL-8)

RN 439798-80-8 CAPLUS

CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6-hydroxy-9-oxo-3-[(propoxycarbonyl)amino]-, 2-(trimethylsilyl)ethyl ester,

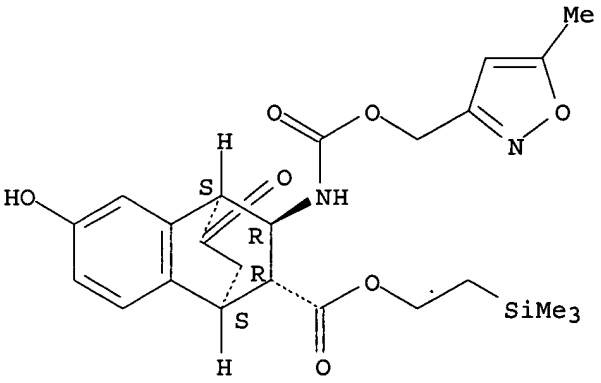
(1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



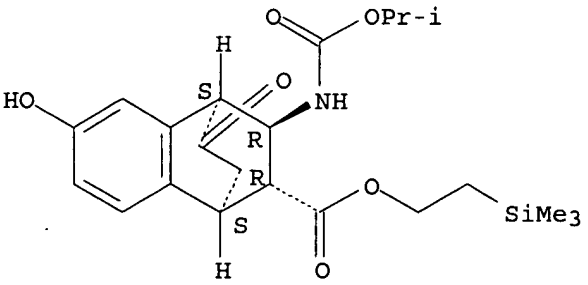
RN 439798-81-9 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6-hydroxy-3-[[[(5-methyl-3-isoxazolyl)methoxy]carbonyl]amino]-9-oxo-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



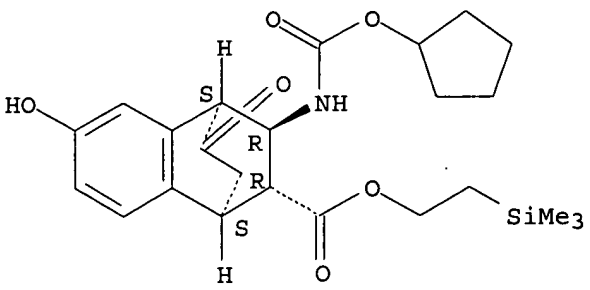
RN 439798-82-0 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6-hydroxy-3-[[(1-methylethoxy)carbonyl]amino]-9-oxo-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



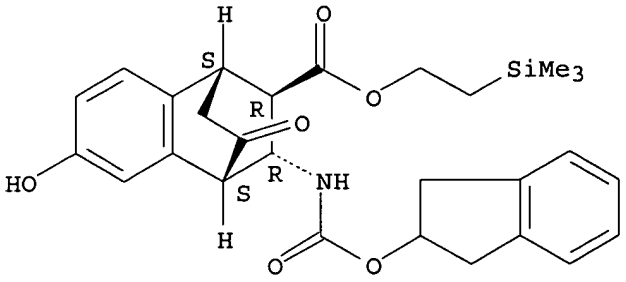
RN 439798-83-1 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 3-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,4-tetrahydro-6-hydroxy-9-oxo-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



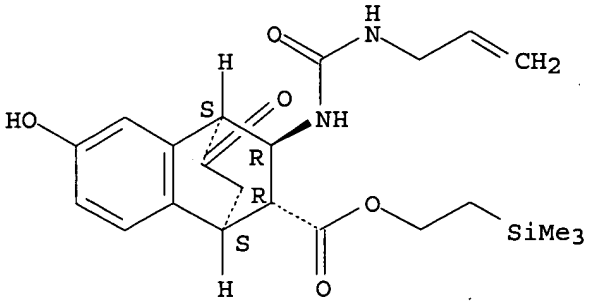
RN 439798-85-3 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 3-[[[(2,3-dihydro-1H-inden-2-yl)oxy]carbonyl]amino]-1,2,3,4-tetrahydro-6-hydroxy-9-oxo-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



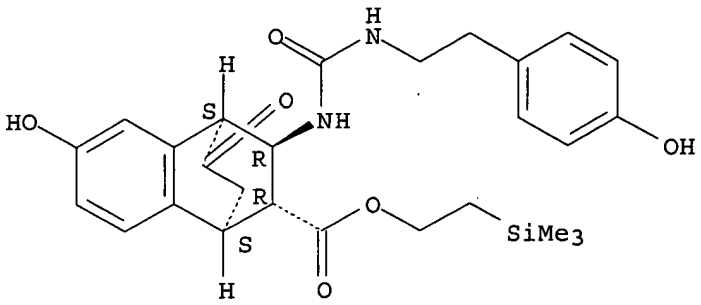
RN 439798-86-4 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6-hydroxy-9-oxo-3-[[(2-propenylamino)carbonyl]amino]-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



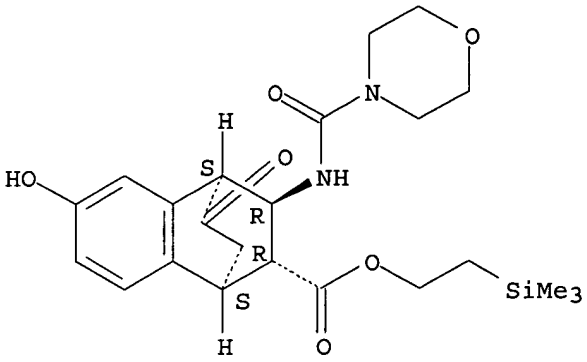
RN 439798-87-5 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6-hydroxy-3-[[[[2-(4-hydroxyphenyl)ethyl]amino]carbonyl]amino]-9-oxo-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



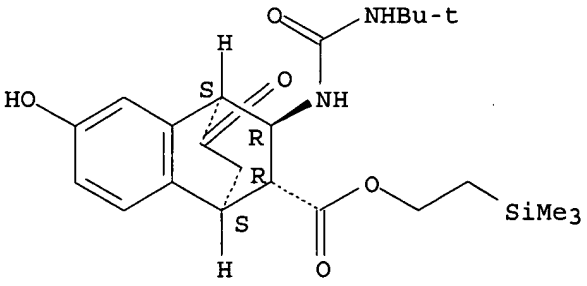
RN 439798-88-6 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6-hydroxy-3-[(4-morpholinylcarbonyl)amino]-9-oxo-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



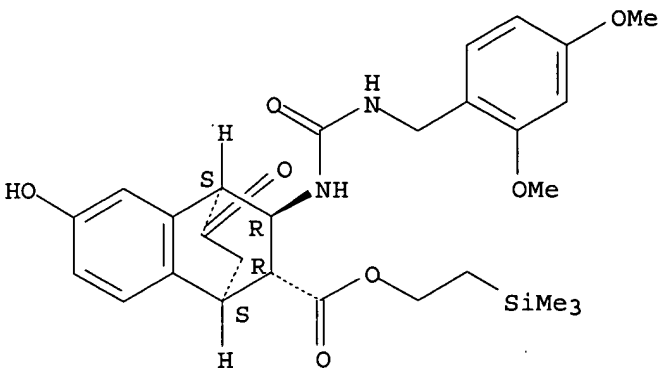
RN 439798-89-7 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 3-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-1,2,3,4-tetrahydro-6-hydroxy-9-oxo-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



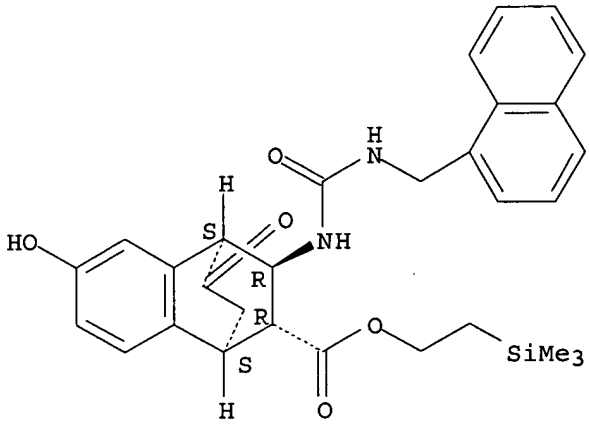
RN 439798-90-0 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 3-[[[[(2,4-dimethoxyphenyl)methyl]amino]carbonyl]amino]-1,2,3,4-tetrahydro-6-hydroxy-9-oxo-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



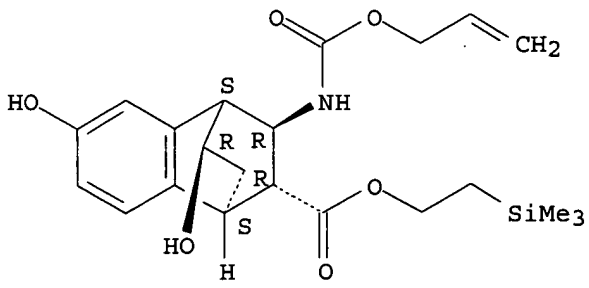
RN 439798-91-1 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6-hydroxy-3-[[[(1-naphthalenylmethyl)amino]carbonyl]amino]-9-oxo-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



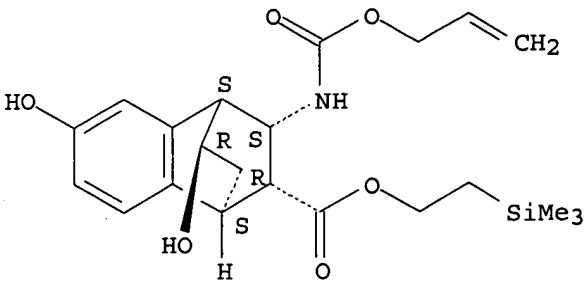
RN 439799-36-7 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6,9-dihydroxy-3-[[(2-propenyloxy)carbonyl]amino]-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R,9S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



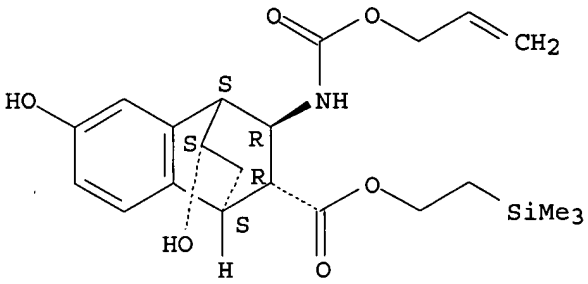
RN 439799-37-8 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6,9-dihydroxy-3-[[(2-propenyloxy)carbonyl]amino]-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3R,4R,9S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 439799-80-1 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6,9-dihydroxy-3-[[(2-propenyloxy)carbonyl]amino]-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R,9R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 439800-25-6 CAPLUS
CN 1,4-Ethanonaphthalene-2-carboxylic acid, 1,2,3,4-tetrahydro-6-hydroxy-9-oxo-3-[[(pentylamino)carbonyl]amino]-, 2-(trimethylsilyl)ethyl ester, (1R,2S,3S,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.